

Primary Neuroendocrine Tumor of the Thymus: Radiological and Pathological Correlation

Kelsey Berman^{1*}, Jacobo Kirsch², Pablo Bejarano³, Ian Drexler², Felipe Martinez²

1. University of South Florida Morsani College of Medicine, Tampa, Florida, USA

2. Imaging Department, Cleveland Clinic Florida, Weston, Florida, USA

3. Pathology Department, Cleveland Clinic Florida, Weston, Florida, USA

* **Correspondence:** Kelsey Berman, 2950 Cleveland Clinic Blvd., Weston, FL 33331, USA
(✉ klberman@usf.edu)

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ABSTRACT

Primary neuroendocrine tumors of the thymus are extremely rare. In this report, we describe a case of a 69 year-old man with an intermediate grade thymic neuroendocrine tumor. The radiologic and histopathologic features of thymic neuroendocrine tumors are discussed with reference to relevant literature.

CASE REPORT

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A 69 year-old man with a past medical history of chronic cough for 9 years and sleep apnea, presented to the emergency room complaining of acute shortness of breath.

The physical exam was unremarkable at that time. AP chest radiograph (not shown) was also unremarkable. Due to clinical concern for pulmonary embolism, the patient underwent further evaluation with chest computed tomography angiography (CTA), which revealed a well-defined, slightly lobulated, approximately 2.4 cm soft tissue attenuation lesion in the anterior mediastinum (Figure 1). Further characterization with mediastinal magnetic resonance (MR) revealed that the lesion had cystic non-enhancing and solid enhancing components and was localized in the expected location of the thymus, Level 3 (Figure 2). No adenopathy was noted. Thymic neoplasm was the working diagnosis. For this reason, the patient underwent bilateral thoroscopic thymectomy.

Gross pathological examination revealed two separate lesions attached to each other. The caudal lesion was a 2.5 cm dark-grown, firm, partially-encapsulated tumor occupying the

lower pole of the thymus (Figure 3). Microscopically, it was an intermediate grade neuroendocrine tumor measuring 2.5 cm in greatest dimension that extended into the surrounding adipose tissue and showed up to 5 mitoses per 10 high power fields in areas. Intratumoral vascular invasion was seen and abundant hemorrhage was noted. Moderate nuclear atypia was present, but necrosis was only focal. The surgical margins and the two lymph nodes resected were free of tumor. The innominate vein margin showed crushed cells of neuroendocrine tumor. Tumor cells were positive for keratin with a perinuclear dot pattern and synaptophysin. They were negative for p63, CD3 and CD20. Ki-67 showed 10% proliferating activity. The second cephalad lesion, located in the upper portion of the thymus, was a benign cyst lined by ciliated epithelium filled with tan, viscous material.

The patient had no post-surgical complications. A Nuclear Medicine Indium-111 Octreotide scan including thoracic and abdomen SPECT was conducted at one year post-surgery and was negative. A CT scan was done at one and a half years after surgery and revealed no evidence of recurrence. 2 years after surgery, there is no evidence of recurrence or progression of disease.

DISCUSSION

Etiology & Demographics:

Thymic neuroendocrine tumors (NET) are potentially aggressive neoplasms capable of local recurrence and distant metastasis. Neuroendocrine tumors are believed to arise from Kulchitsky cells. They are rare tumors of the anterior mediastinum with an annual incidence estimated at 0.01/100,000 [1]. Thymic NETs comprise less than 5% of epithelial tumors in the thymus [2]. Approximately 400 cases of thymic NET have been reported in the literature.

The most current World Health Organization (WHO) histological classification is essentially an extrapolation of the pulmonary NETs, and they can be classified into low-grade typical carcinoid, intermediate-grade atypical carcinoid, and the high-grade large cell and small cell carcinoma [3, 4]. Several stage classifications for thymic NETs have been proposed. In the past, the International Thymic Malignancies Interest Group utilized the Masaoka staging system modified by Koga, known as the Masaoka-Koga staging system [5]. Surveillance, Epidemiology, and End Results (SEER) proposed another staging system that takes into account the extension of disease: localized, regional, or distant [6]. However, the 8th edition of the TNM (tumor nodes metastases) classification of thymic tumors has recently been approved by the American Joint Committee on Cancer and the Union for International Cancer Control. This system is helpful in classifying NETs that produce hematological and lymphogeneous metastases, as well as in clarifying treatment options by setting guidelines that delineate which tumors are resectable [7]. Specifically, this system addresses invasion into local structures (T component), lymph node involvement (N component), and presence of nodules and/or distant organ metastases (M component). The result of this new staging system is improved classification, as well as more precise therapeutic and prognostic guidelines [8, 9].

Neuroendocrine tumors of the thymus are found predominantly in males, with a male to female ratio of 3:1 [10]. They are most common in white males and are typically seen in the fourth or fifth decades of life, with 58 years as the average age of onset [6, 11].

Clinical & Imaging Findings:

Thymic NETs can be asymptomatic and discovered incidentally, can present with symptoms related to local growth, or can present with endocrine abnormalities such as paraneoplastic syndromes [12]. Approximately 50% of thymic neuroendocrine carcinomas are functionally active. They can secrete precursors of serotonin such as adrenocorticotrophic hormones, which are found in approximately 40% of the cases. In these cases, the excess ACTH secreted by the tumor can lead to Cushing's Syndrome, and possibly to bilateral adrenal hyperplasia [13]. Rarely, Growth Hormone-Releasing Hormone secretion has been described leading to acromegaly [14]. Non-functioning thymic neuroendocrine carcinomas may be related to multiple endocrine neoplasia. These tumors, originating in the anterior mediastinum, are often asymptomatic, but may rarely present with non-specific symptoms of mediastinal involvement such as chest pain,

dyspnea, cough, shortness of breath, hoarseness or pneumonia. Carcinoid syndrome is extremely rare as serotonin levels are usually low with these tumors.

Histopathological analysis of thymic NETs may reveal a number of unusual appearances such as spindle cell features, abundant oncocytic cytoplasm, mucin-rich stroma or microfilamentous inclusions. Cells are dispersed in solid sheets, which merge with areas of rosette-like structures, ribbon-like growth patterns, or organoid nests of cells (Zellballen) surrounded by fibrovascular septa [15, 16, 17]. The cells are polygonal with central rounded nuclei. They may have foci of necrosis or calcifications [10].

Immunohistochemistry is pivotal in diagnosing neuroendocrine tumors, with the most common markers being synaptophysin, chromogranin A, cytokeratin, and CD56. Thymic NETs test negative for GATA-3 and napsin A. Some of these tumors, in particular high-grade tumors, may also test positive for TTF-1, creating confusion with pulmonary carcinomas [18]. Contrary to neuroendocrine thymic carcinomas, mediastinal paraganglioma do not stain for cytokeratin. Non-neuroendocrine mediastinal neoplasms' lack of immunoreactivity for neuroendocrine markers is a key in the differential diagnosis [15].

Though no definite conclusions have been drawn, some research has been conducted in an attempt to identify genes linked to thymic NETs. In cases related to multiple endocrine neoplasia syndrome type 1, mutations in several introns and exons of the MEN1 gene have been implicated [19]. In two other studies, a variety of chromosomal imbalances (both gains and losses) were found, with high-grade thymic NETs exhibiting the greatest number of alterations [2, 20]. Among thymic NETs that secrete ACTH, regulatory changes have been found in the Wnt and Notch pathways, as well as CDC25B, CTBP, and CTNNB1, among others [21].

Thymic NETs are classified as low-grade, intermediate-grade, and high-grade according to the WHO [3]. Low- and intermediate-grade tumors with mitotic figures are divided into two categories: typical carcinoid with less than 2 mitoses per 10 high power fields (HPFs) and absence of necrosis, and atypical carcinoid with 2-10 HPFs and the presence of necrosis [3, 22, 23]. The reported case corresponds to an atypical carcinoid. High-grade tumors are categorized, whereas there is presence of small or large cell cytology: small cell carcinoma and large cell neuroendocrine carcinoma [3, 4, 23, 24]. Small cell carcinomas are a particularly malignant, rapidly metastasizing form of high-grade NET that typically form in the anterior-middle mediastinum. This type of NET tends to generate large tumors that can invade nearby tissues. These factors, in conjunction with their high growth fraction and poor differentiation, contribute to the low survival rates associated with small cell carcinomas [25].

The appearance of thymic NETs on CT is non-specific and typically demonstrates a large, well-circumscribed mass of heterogeneous attenuation in the anterior mediastinum. Thymic NETs are enhancing soft tissue density masses that may or may not demonstrate cystic changes. Necrosis,

hemorrhage, and calcification may also be present [26]. They may metastasize to the adrenal glands and bones. Additionally, there may be extension into the lungs, liver, pericardium, and local blood vessels and lymph nodes, which may also cause SVC invasion and obstruction [13]. On MRI, these tumors are enhancing masses that usually demonstrate heterogeneous signal intensity and various degrees of cystic changes and enhancement. Thymic NETs can also be slightly T1 hyperintense or hypointense. On FDG-PET, thymic NETs are FDG-avid and may appear similar to their non-neuroendocrine counterparts (which have a typical SUV max of 7.6 to 10.5) [27]. However, ⁶⁸Ga-DOTATATE-PET may prove a more useful modality for neuroendocrine tumors, as one study found that this type of PET scan detected additional thymic NET lesions that were not visible on FDG-PET [28].

Differential Diagnoses:

The most significant imaging differential considerations of thymic NETs include thymoma, teratoma, diffuse large cell lymphoma, and non-neuroendocrine thymic carcinoma. Additional considerations include hemangioma, bronchopulmonary carcinoid tumor, intrathoracic goiter, seminoma and mediastinal paraganglioma. Based on imaging alone, thymic NETs are difficult to differentiate from other anterior mediastinal masses such as thymomas and thymic carcinomas, hence pathological evaluation is necessary to make the diagnosis.

Thymoma

Thymomas are the most common tumors found in the anterior mediastinum and affect between 1 and 5 Americans per million each year. These tumors tend to occur at similar rates in males and females, and typically affect Asians and African Americans more than other groups [29]. The average age of onset for thymomas is between the fifth and seventh decades of life, though African Americans tend to experience an earlier onset of disease (about ten years earlier than whites) [30]. Clinically, thymomas are slow-growing but invasive, and can be accompanied by symptoms such as cough, shortness of breath, and chest pain. Additionally, about 30-50% of patients with thymomas will also experience symptoms of myasthenia gravis [29]. On MRI, thymomas are homogenous, enhancing mediastinal masses. They are slightly T1 hypointense and show no evidence of fat suppression on both in-phase and out-of-phase imaging. On CT, thymomas are homogeneously-enhancing soft tissue density masses. On FDG-PET, thymomas usually show significant FDG-accumulation, which can help differentiate them from thymic cysts, which tend to show little to no FDG-accumulation. Low-grade thymomas generally have an SUV max between 2.0 and 4.0, while high-grade thymomas tend to have a slightly higher SUV max (4.0 to 7.4) [27].

Teratoma

Teratomas are germ cell tumors consisting of cells from multiple embryonic germ lines. They usually affect children and young adults, with a typical age of onset prior to 40 years [31]. Teratomas appear as enhancing, T1 hypointense masses on MRI. They may or may not display cystic changes, calcifications, and fatty components. On CT, teratomas are soft tissue density enhancing masses with or without cystic

changes, calcifications, and fat. On FDG-PET, some teratomas may show slight FDG-accumulation, while others show no avidity [27].

Lymphoma

Both Hodgkin and non-Hodgkin lymphoma can affect thymic tissue, but thymic and mediastinal involvement are more characteristic of Hodgkin lymphoma. Hodgkin lymphoma occurs most typically in young adults and adults in their fifth decade, and though it is more common in women, thymic involvement is more common in men. Non-Hodgkin lymphoma, on the other hand, is most common in older men, though some subtypes also affect young women and young men [31]. On MRI, lymphomas are faintly T1 hypointense, homogeneously enhancing mass. Lymphomas are soft tissue density, homogeneously enhancing masses on CT. On FDG-PET, malignant lymphomas are FDG-avid with typical SUV max values of greater than 6.0 [27].

Non-Neuroendocrine Thymic Carcinoma

Thymic carcinomas are rare, aggressive neoplasms that often present with local invasion, metastases, and/or lymph node involvement upon diagnosis. The average age of onset for these tumors is between 47 and 60 years, and they tend to occur more frequently in males than females [32]. On MRI, thymic carcinomas look similar to thymic NETs, appearing hyperintense on both T1- and T2- weighted images. Necrosis, hemorrhage, and cystic changes may also occur with thymic carcinomas, which can result in heterogeneous enhancement [29]. On CT, thymic carcinomas often have irregular borders and a heterogeneous appearance, sometimes accompanied by cystic changes and necrosis [33]. On FDG-PET, thymic carcinomas show strong FDG-accumulation, with a typical SUV max range of 7.6 to 10.5 [27].

Treatment & Prognosis:

Thymic NETs behave in a malignant manner in 80% of cases [11]. Therefore, surgical excision is the treatment of choice. Complete resection is often challenging as these tumors may present with invasion of adjacent structures and distant metastases. These tumors respond poorly to radiotherapy. Surgical excision appears to be the only effective treatment [34]. Additionally, among surgical treatments, resection appears to have better survival rates than debulking [35].

Prognostic factors have been discussed in the literature. The International Thymic Malignancies Interest Group has highlighted the value of tumor stage and completeness of resection in the prognosis of these tumors. In the SEER study and in the study directed by Cardillo et al., tumor size was the only statistically significant prognostic factor for thymic neuroendocrine tumors, with significant cutoff sizes of greater than 5 cm and 7 cm, respectively [15]. Among other prognostic factors, Ki67 expression has been considered, as it is a well-known prognostic factor in neuroendocrine tumors, as well as histologic grading or Masaoka-Koga staging and distant metastases [36]. More recently, according to Sullivan and Weksler's 2017 findings, surgical resection, tumor size, and Masaoka-Koga stage were statistically significant

predictors of survival, while tumor grade appeared an unimportant factor [35].

Thymic NETs tend to be more aggressive than lung NETs. According to previous studies, tumors associated with endocrinopathies also tend to behave more aggressively than tumors unaccompanied by endocrinopathies [5, 37]. Metastasis and recurrence of thymic NETs is not unusual, and both intra- and extra-thoracic metastases have been documented in the literature [38]. A recent paper showed that among the two types of high-grade carcinomas of the thymus, the 5-year survival rate was 30% for large cell and 0% for small cell, as opposed to the 100% and 50% rates found for lower grade typical and atypical carcinoids, respectively [2].

In conclusion, we describe the imaging and pathological features of a thymic NET, which is a rare entity. This aggressive tumor is slow-growing, and commonly invades adjacent tissues. Local recurrence may occur years later.

TEACHING POINT

Primary neuroendocrine tumors of the thymus are aggressive neoplasms found in the mediastinum. Typically, thymic neuroendocrine tumors appear as large, heterogeneous masses in the anterior mediastinum on CT, and demonstrate heterogeneous signal intensity on MRI.

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FIGURES

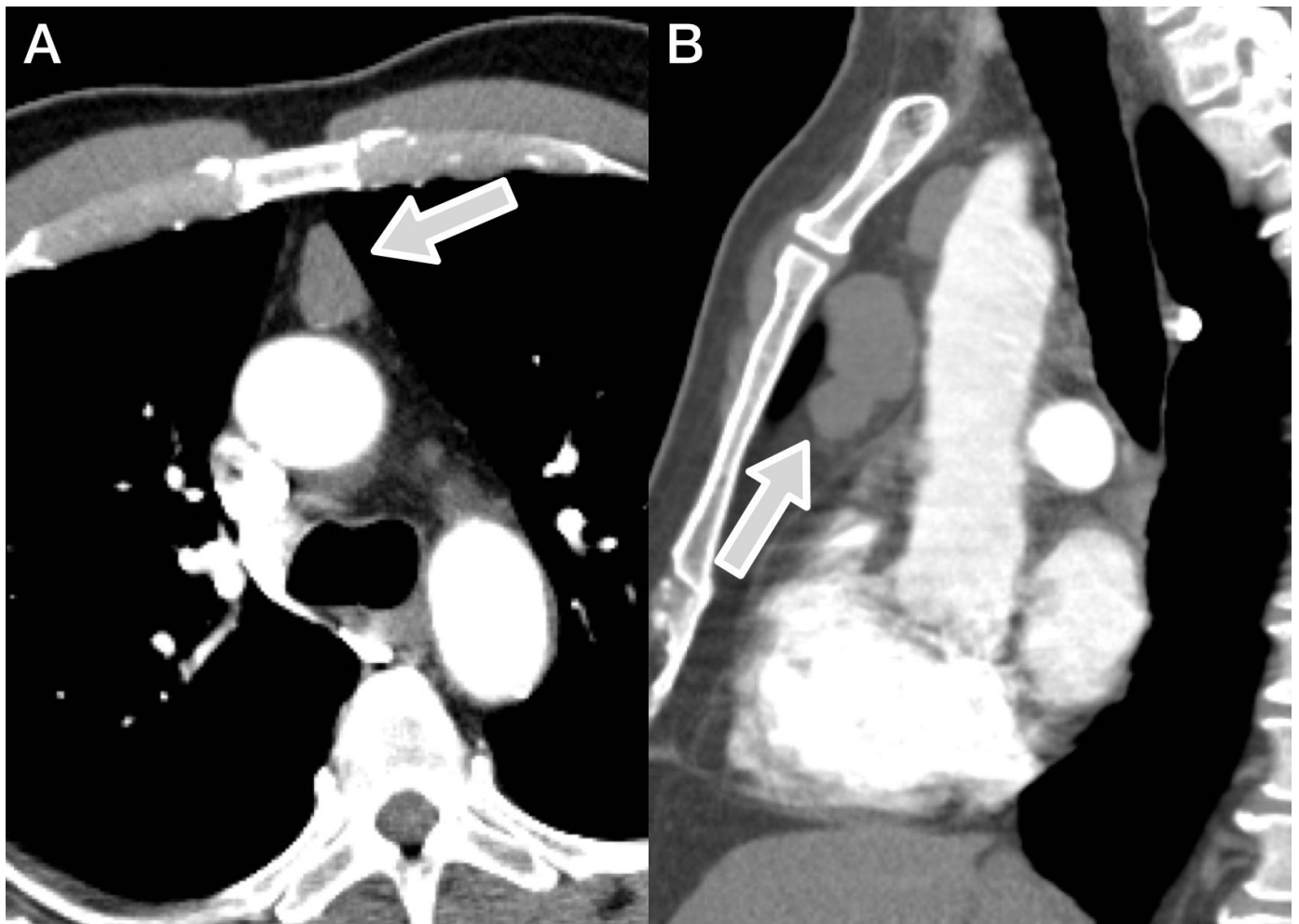


Figure 1: 69 year-old male with an intermediate grade thymic neuroendocrine tumor.

FINDINGS: CT scan of the chest after intravenous contrast administration. Axial (A) and sagittal (B) images demonstrating a well-defined, slightly lobulated, soft tissue attenuation mass in the anterior mediastinum - level 3 (arrows). No mediastinal adenopathy.

TECHNIQUE: Chest CT scan (Siemens 64 channel) with IV contrast (Omnipaque - 350, 150 cc), standard protocol. KVP: 120, MAS: 140, Total DLP: 371 mGy/cm, axial slice thickness: 3mm, sagittal slice thickness: 3mm.

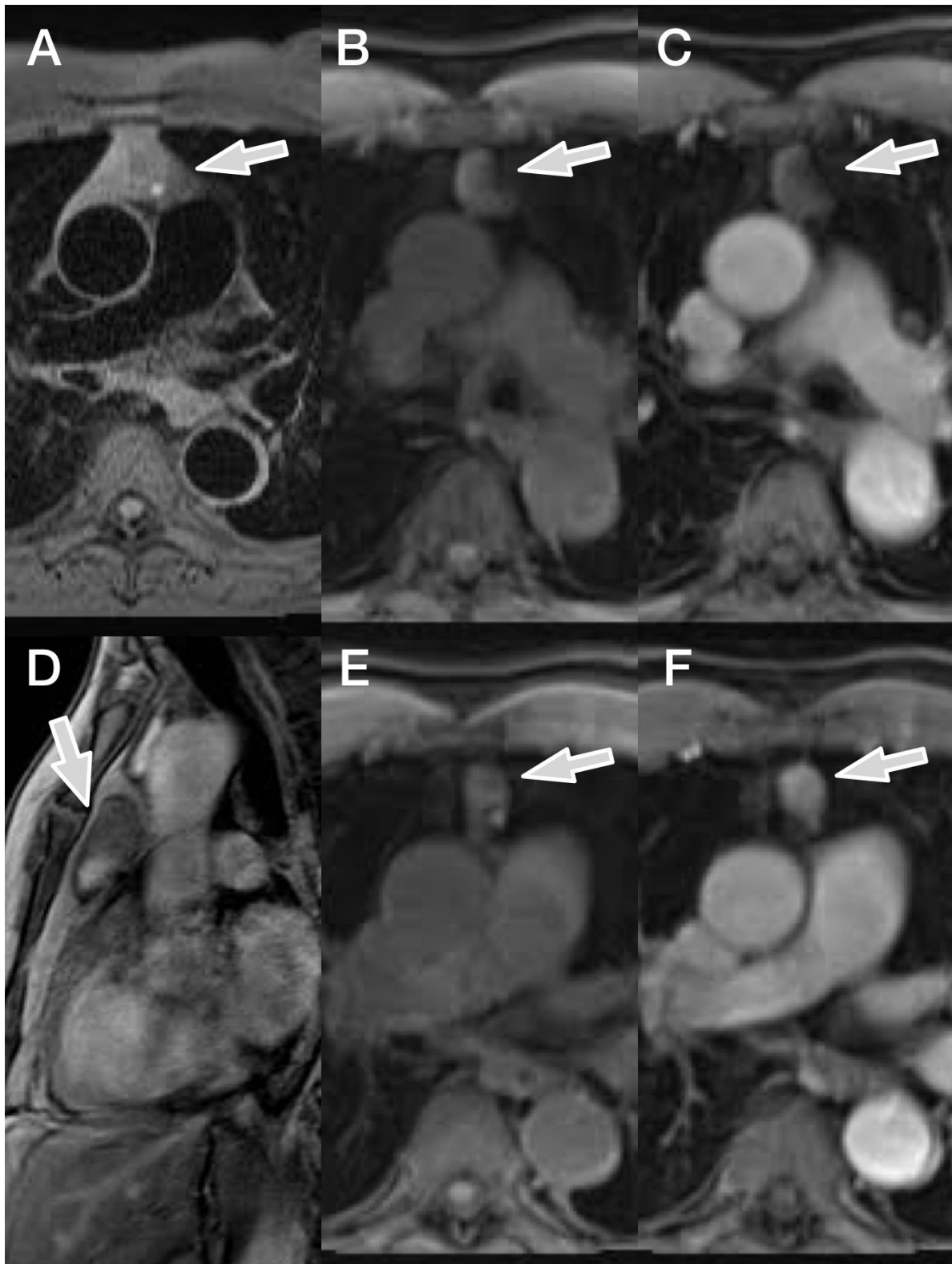


Figure 2: 69 year-old male with an intermediate grade thymic neuroendocrine tumor.

FINDINGS: MR of the mediastinum before and after administration of gadolinium-based contrast demonstrating a partially cystic and solid enhancing mass in the anterior mediastinum level 3 corresponding to lesion seen on CT (Figure 1). Axial T1 fat sat image through cephalad portion (A) shows the lesion to be T1 hyper-intense, suggesting proteinaceous cystic component (arrow). Axial VIBE T1 images through cephalad portion of the lesion before (B) and after IV contrast administration (C) showing no enhancement (arrow). Sagittal VIBE T1 image after IV contrast (D) demonstrating non-enhancing cephalad and enhancing/solid caudal components (arrow head). Axial VIBE T1 images through the caudal solid portion of the lesion before (E) and after IV contrast administration (F) showing avid enhancement (arrow head).

TECHNIQUE: T1 weighted images with and without gadolinium-based contrast (Dotarem 20cc) with a 1.5 Tesla scanner.

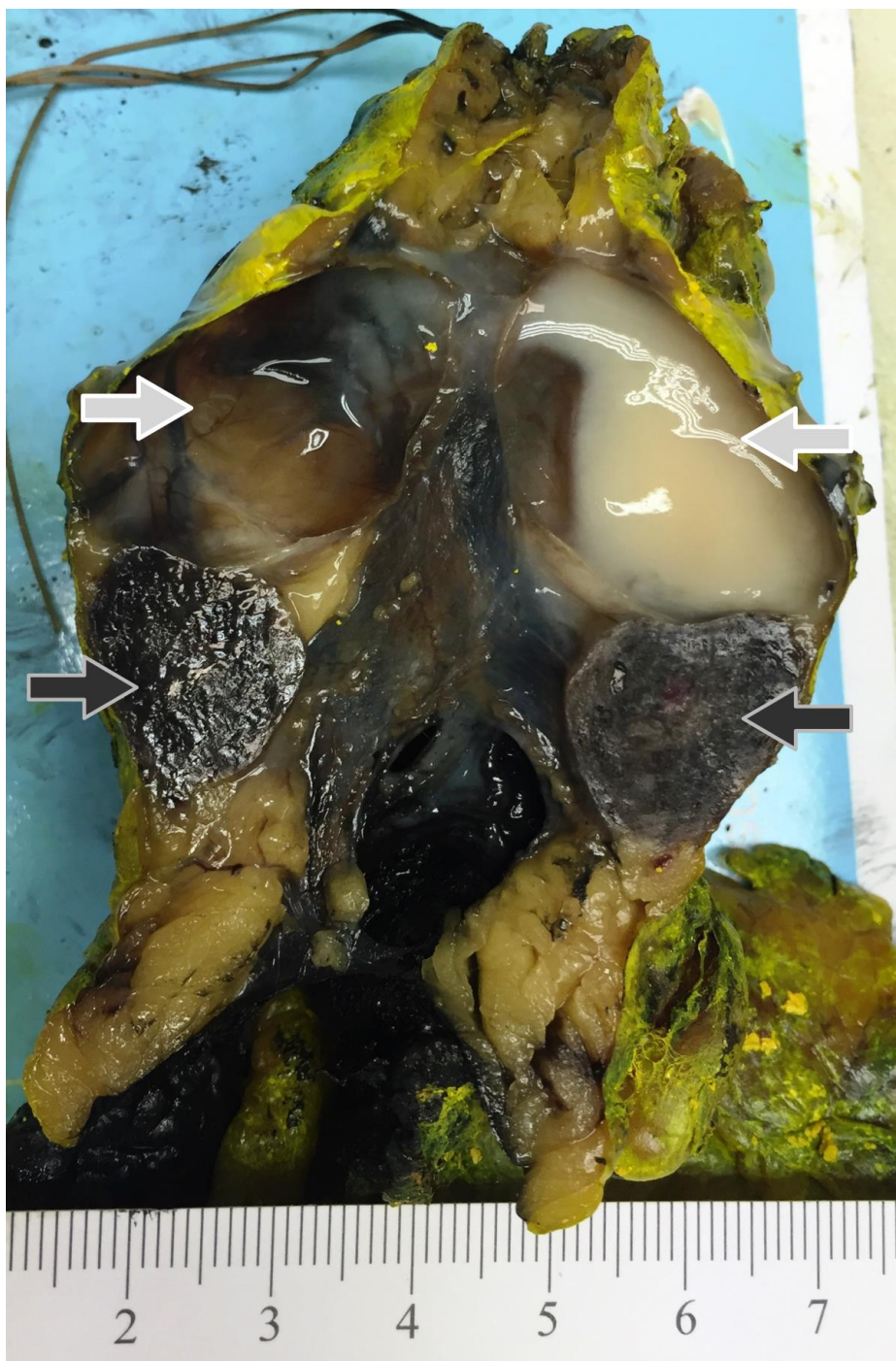


Figure 3: 69 year-old male with an intermediate grade thymic neuroendocrine tumor.

Gross pathology: Bi-halved specimen showing a cyst in the upper pole (white arrows) filled with tan-brown viscous material. Caudally, a red-brown homogenous mass (black arrows) corresponding to the neuroendocrine tumor that extends into the surrounding adipose tissue.

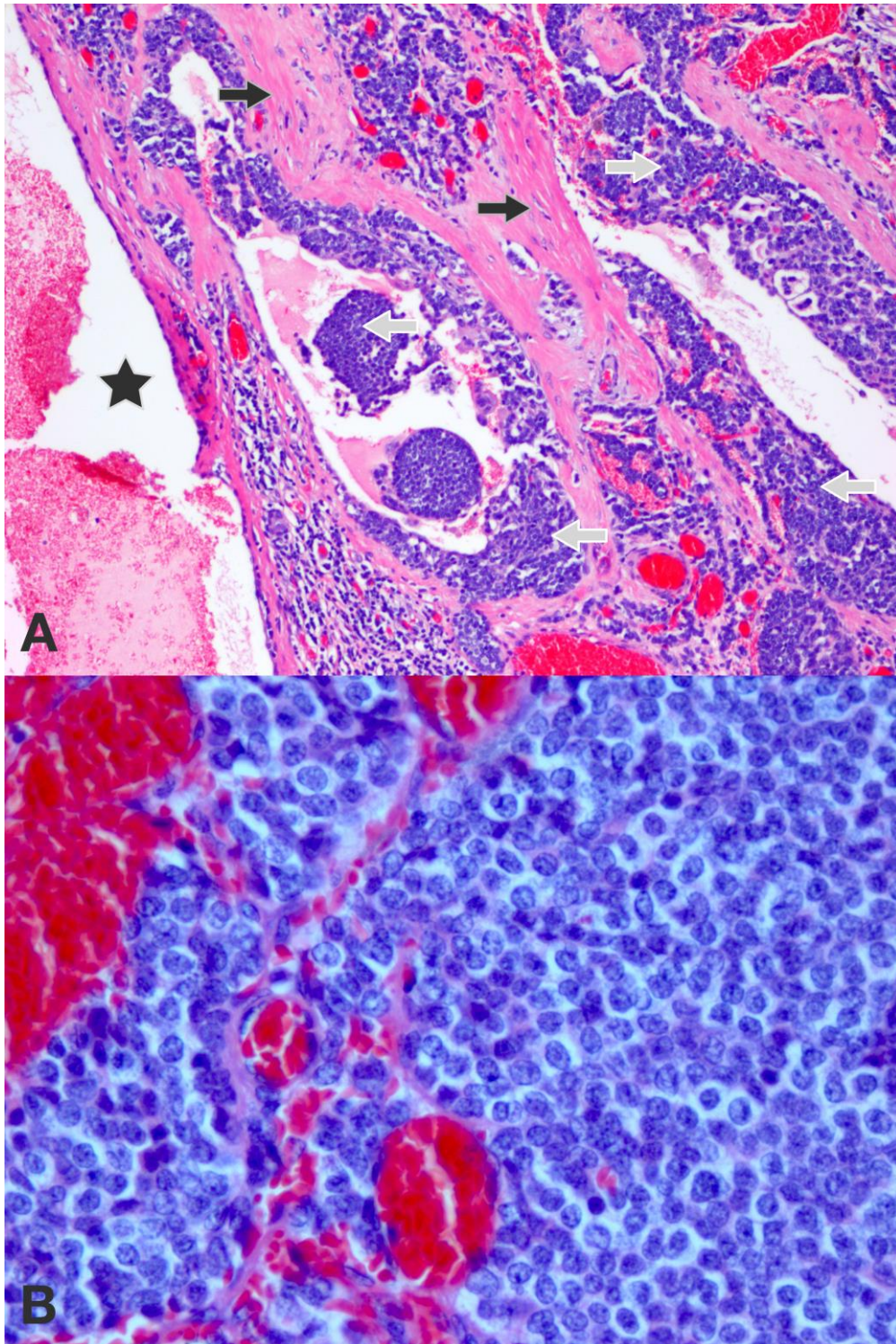


Figure 4: 69 year-old male with an intermediate grade thymic neuroendocrine tumor.

A: Nests of tumor cells (white arrows) separated by fibrous bonds (black arrows). At the left (star), a cyst lined by flat epithelium. Hematoxylin and eosin (x200).

B: Monotonous population of cells in a vascular background showing round nuclei with irregular nuclear membrane, stippled chromatin and subtle nucleoli. Hematoxylin and eosin (x400).

Etiology	Neoplasm caused by Kulchitsky cells
Incidence	0.01 out of 100,000 annually
Gender Ratio	3:1 (male: female)
Age Predilection	Forties and fifties (with an average age of onset of 58 years)
Risk Factors	Age, endocrine abnormalities
Treatment	Debulking or surgical excision (with excision being the more effective option when possible)
Prognosis	High-grade large cell carcinoma: 30% 5-year survival High-grade small cell carcinoma: 0% 5-year survival Typical carcinoid: 100% 5-year survival Atypical carcinoid: 50% 5-year survival
Imaging Findings	On CT: nonspecific, large, well-circumscribed mass of heterogeneous attenuation in the anterior mediastinum. On MRI: heterogeneous signal intensity with various degrees of cystic changes and enhancement. On PET: FDG-avid, with potential visualization of additional lesions with 68Ga-DOTATATE-PET.

Table 1: Summary table for Thymic Neuroendocrine Tumor

	MRI	CT	PET
Thymic neuroendocrine tumor	Enhancing mass slightly T1 hyperintense or hypointense mass, with or without cystic components	Enhancing soft tissue density mass with or without cystic components	FDG-avid, but 68Ga-DOTATATE-PET may be preferable to detect additional lesions not visible on FDG-PET
Thymoma	Homogenously enhancing, slightly T1 hypointense mediastinal mass with no evidence of fat suppression on in-phase and out-of-phase imaging	Homogenously enhancing soft tissue density mass	FGV-avid Low-grade thymomas: SUV max between 2.0 and 4.0 High-grade thymomas: SUV max between 4.0 and 7.4
Teratoma	Enhancing T1 hypointense mass with or without cystic changes and presence or absence of calcifications and fatty components	Soft tissue density enhancing mass with or without cystic changes in calcifications and fat	Some may show slight FDG-avidity, while others show none
Lymphoma	Faintly T1 hypointense, homogenously enhancing mass	Soft tissue density, homogenously enhancing mass	FDG-avid, SUV max greater than 6.0
Non-neuroendocrine thymic carcinoma	Heterogeneously enhancing hyperintense mass on both T1 and T2, with or without necrosis, hemorrhage, and cystic changes	Heterogeneously enhancing mass, usually with irregular borders, with or without cystic changes and necrosis	Strong FDG-avidity, SUV max between 7.6 and 10.5

Table 2: Differential diagnosis table for Thymic Neuroendocrine Tumor

ABBREVIATIONS

ACTH = Adrenocorticotropic hormone
CT = Computed tomography
CTA = Computed tomography angiography
FDG-PET = Fluorodeoxyglucose-positron emission tomography
68Ga-DOTATATE-PET = Gallium-68-DOTA-octreotate-positron emission tomography
MRI = Magnetic resonance imaging
NET = Neuroendocrine tumor
PET = Positron emission tomography
SEER = Surveillance, Epidemiology, and End Results
SUV max = maximum standardized uptake value
SVC = Superior vena cava
WHO = World Health Organization

KEYWORDS

Thymic neuroendocrine tumor; Thymic neoplasm; Thymus; Mediastinum; Magnetic resonance imaging; MRI; Computed tomography angiography; CTA; Positron emission tomography; PET

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